REMARKS

Claims 1, 3, 5-10, 22 and 23 are pending after entry of the amendment. Claims 1-10 were examined and rejected.

Figure 8 is amended to show hatched bars.

Claim 1 is amended to delete the phrase "for identifying an anti-viral agent" and to specify that the NS4B nucleotide binding motif (NBM) polypeptide is Hepatitis C Virus NS4B nucleotide binding motif (NBM) polypeptide. Claim 5 is amended to clarify claim language and to delete the term "activity". Claims 22 and 23 are newly added. Support for new claims 22 and 23 is found on page 22, lines 13-20. No new matter is added.

Claims 2 and 4 have been cancelled without prejudice.

Reconsideration of claims 1, 3, 5-10, 22 and 23, the only claims pending in the application is respectfully requested.

DRAWINGS

The drawings are objected to because Figure 8 is missing the hatched bars that are described in the specification.

Appropriate corrections have been made in Fig. 8. A replacement sheet for Fig. 8 is provided.

The Applicants believe that this objection has been addressed and may be withdrawn. Withdrawal of this objection is requested.

CLAIM REJECTIONS-35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-10 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. It is alleged that the method steps are not correlated with the agent's status as an anti-viral agent.

Without any intention to agree with this rejection and solely to expedite prosecution, the phrase "for identifying an anti-viral agent" in the preamble of claim 1 has been deleted.

The Applicants submit that in view of this amendment, the 35 U.S.C. § 112, second paragraph rejection is now moot and may be withdrawn.

Claim 4 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. It is alleged that claim 4 fails to further limit claim 1.

Without any intention to acquiesce to the correctness of this rejection and only to expedite prosecution, claim 4 has been cancelled without prejudice.

In view of this amendment, the 35 U.S.C. § 112, second paragraph rejection is now moot and may be withdrawn.

Claim 5 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. It is stated that it is not clear what "an RNA binding activity" is and whether the claim requires a determination as to effect of the test compound on an activity of NS4B that involves RNA-binding.

Without any intention to agree to the correctness of this rejection and solely to expedite prosecution of this case, claim 5 has been amended to recite that "said method further comprises determining an effect of said candidate agent on RNA binding of said polypeptide".

The Applicants submit that in view of the amendments, § 112, second paragraph rejection does not apply and may be withdrawn.

Withdrawal of this rejection is respectfully requested.

CLAIM REJECTIONS-35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1 and 3-10 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Applicants respectfully traverse this rejection.

Without agreeing with the correctness of this rejection and solely to expedite prosecution, claim 1 has been amended to recite the subject matter of claim 2, i.e., a

"hepatitis C virus (HCV) NS4B nucleotide binding motif (NBM) polypeptide", which is not encompassed by this rejection.

The Applicants believe that this rejection is moot and may be withdrawn.

Claim 5 is rejected as it is allegedly not clear what activity the polypeptide is performing that results in RNA-binding.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 5 is amended to cancel the term "activity".

The Applicants believe that this rejection has been adequately addressed and may be withdrawn.

CLAIM REJECTIONS-35 U.S.C. § 103

Claims 1-4 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Del Vecchio et al (WO 99/01582) in view of teachings of Jin et al (Arch Biochem Biophys 20: 47-53), Kadare et al (J Virol 70: 8169-74), and Rodriguez et al. (JBC 268: 8105-10). The Applicants respectfully traverse this rejection.

The Patent Office has recently published guidelines for determining obviousness under 35 U.S.C. §103 in view of the KSR decision. These guidelines, termed the "Obviousness Guidelines" are found in the Federal Register Vol. 72, No. 195 (published Wednesday, October 10, 2007) and should be followed by Examiner in evaluating whether a claim is obvious.

According to the Obviousness Guidelines, when Office personnel reject claims by attempting to combine prior art elements according to allegedly known methods to yield predictable results, the Office must resolve the Graham factual inquiries and articulate:

(1) "a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;"

(2) "a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately; and"

(3) "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, citing KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395 (US 2007).

Thus, the rationale to support a conclusion that a claim would have been obvious is that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions," and that "the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention." Id. at 57529.

This rejection is based on the idea that Del Vecchio's NS4B-based ATPase assay, in combination with Jin, Kadare and Rodriguez' disclosure that ATPases can also have GTPase activity, renders the claims obvious. As best understood by the Applicants, the Examiner believes that Jin, Kadare and Rodriguez' teachings would lead one of skill in the art to believe that NS4B, in addition to having ATPase activity, would also have GTPase activity. Thus, one of skill in the art would be motivated to screen for anti-viral inhibitors using the GTPase of NS4B.

Del Vecchio discloses that the NS4B protein of Hepatitis C Virus has ATPase activity, and that the NS4B's ATPase activity requires the nucleotide binding motif of that protein. Del Vecchio neither discloses that NS4B protein has GTPase activity nor provides any teaching that would lead one of skill in the art in that direction. Del Vecchio further teaches screening methods to identify molecules that activate or inhibit the ATPase activity of NS4B. According to Del Vecchio, inhibitors of NS4B's ATPase activity can be used as antiviral compounds. Del Vecchio neither teaches screening for inhibitors of NS4B's *GTPase* activity nor provides any reason to do so.

In order to meet Del Vecchio's deficiencies, the Examiner cites three references: Jin, Kadare, and Rodriguez. According to the Examiner Jin teaches that the NTPase of HCV NS3 protein has the ability to act on both ATP and GTP, and each of Kadare and Rodriguez teach proteins that contain a nucleotide binding motif allegedly similar to the motif described by Del Vicchio, that are also able to hydrolyze both ATP and GTP. The Examiner alleges that in view of these teachings there would have been a reasonable

expectation that the HCV NS4B protein would also have GTPase activity, and that one of skill in the art would have a reason to screen for anti-viral agents that inhibit that activity.

The Applicants believe that it is not possible to predict that a NS4B has a GTPase activity in addition to an ATPase activity for the following reasons:

1. not all ATPases have GTPase activity;
2. one of the ATPases cited in this rejection as having both ATPase and GTPase activities (i.e., Rodriguez' ATPase) actually only appears to have ATPase, and not GTPase, activity;
3. NS4B's overall structure and nucleotide binding sequence is significantly different to known ATPases and GTPases, and hence a GTPase activity could not have been definitively predicted from its structure at the time of filing.

While the Applicants agree that certain proteins have ATPase and GTPase activity, a detailed review of the art reveals that one of skill in the art would not automatically expect every ATPase to have GTPase activity. As such there would be no expectation of success - a cornerstone of Federal Circuit case law and the recent KSR decision – that NS4B has a GTPase activity.

A detailed review of related literature and the references cited by the Examiner reveals that it does not necessarily follow that a protein that has been identified as an ATPase will also be a GTPase. In particular, the report by Rodriguez (as cited by the Examiner in support of this rejection) that Poliovirus protein 2C has ATPase and GTPase activities appears to have been negated by Pfister et al. (J. Biol. Chem, 274, 11, 6992-7001, 1999; Exhibit A). Similar to Rodriguez, Pfister shows that the nucleotide binding motif of Poliovirus protein 2C binds and hydrolyses ATP. However, Pfister goes on to report that other NTPs, including GTP, while being able to bind competitively to protein 2C, are poor substrates for hydrolysis (See abstract and section titled "ATP is the preferred substrate for GST-2C" on page 6995). Thus, in contrast to the report by Rodriguez, protein 2C has an ATPase activity but no GTPase activity, although both ATP and GTP bind to the protein. Similarly, Umezu et al (Proc. Natl. Acad. Sci 87:5363-5367, 1990; Exhibit B) report that the Rec Q helicase exhibits ATPase but no GTPase activity (see first column, third paragraph, page 5365). One of skill in the art would look at this literature and have no reasonable expectation that since NS4B has ATPase activity it

would necessarily have GTPase activity. Rather the protein would have to be tested to determine if it has a GTPase activity.

The Applicants arguments are bolstered by the fact that the NS4B's overall structure and the amino acid sequence immediately adjacent to its nucleotide binding motif are extremely unusual for an ATPase or a GTPase. NS4B proteins are typically characterized by an N-terminal amphipathic helix, at least two transmembrane domains, and a nucleotide binding motif, where the nucleotide binding motif facilitates nucleotide binding and hydrolysis. This structure appears to be unique among NTPases. Moreover, the amino acid sequences immediately adjacent to either side of the nucleotide binding motif region are very different from that of other ATP or GTP-binding proteins. NS4B's uniqueness and the lack of any structure/function relationship information on NS4B decreases the possibility that the GTPase activity could have been predicted with a reasonable expectation of success. In other words, NS4B looks very different to known ATPases that have GTPase activity and, as such, there is no reason to suspect that it has both of these activities.

Furthermore, even if it could have been predicted that NS4B has GTPase activity, none of the cited references individually or in any combination provide a reason to perform GTPase assay. The "Obviousness Guidelines" state "[It] can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements the way the claimed new invention does". KSR, 550 U.S. at , 82 USPQ2d at 1396. Since such a reason is not provided in the cited prior art, they cannot be used to make the instant invention obvious.

Moreover, without any intention to discredit Del Vecchio's work, the Applicants believe that Del Vecchio discovered a side-activity of NS4B that may or may not be biologically relevant. The Applicants on the other hand discovered that NS4B's major activity is a GTPase activity. This position is based on data shown in Figure 3B of the specification. Figure 3B shows that the GTP binding activity of NS4B is much higher than the ATP binding activity (see also Fig. 3B, the description on page 3, lines 22-26 and methods on page 38, lines 10-15 of the specification).

Since NS4B's major activity is a GTPase activity, the Applicants believe that the claimed screening assay would identify more effective anti-viral agents than the assay

described in Del Vecchio. Along these lines, the Applicants note that it is common to find ATPase inhibitors that do not inhibit the GTPase activity. For example, Tate et al. (J. Biol. Chem, 266, 24, 16165-16170, 1991, Exhibit C) report that the ATPase activity, but not GTPase activity of certain proteins can be inhibited. Thus, without the Applicants' discovery, inhibitors for NS4B's major activity would not be discovered.

In summary, based on a careful review of the cited references as well as related literature, it is clear that one of skilled in the art would not expect to practice the claimed method with a reasonable expectation of success. Indeed, no such claim was made by Del Vecchio. Thus the cited references do not make the claims obvious. The Applicants submit that this rejection has been adequately addressed and may be withdrawn.

Claims 6 and 7 are rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Del Vecchio in view of Jin, Kadare, and Rodriguez and further in view of Morouianu et al. (PNAS 92:4318-22).

Claims 6 and 7 are drawn to the method of claim 1 and require the candidate agent to be a nucleotide analog and a non-hydrolysable nucleotide analog, respectively.

The teachings of Jin, Kadare, and Rodriguez are discussed above. Morouianu is cited for its teachings of non-hydrolysable nucleotide analogs capable of inhibiting the activity of a GTPase protein.

As established in the foregoing discussion, as applied to claims 1-4, Del Vecchio in view of Jin, Kadare, and Rodriguez do not render claims 6 and 7 obvious. Morouianu fails to correct the deficiencies of these references and hence can not be used to establish a prima facie case of obviousness. As such this rejection should be withdrawn.

Withdrawal of this rejection is requested.

Claims 8-10 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Del Vecchio in view of Jin, Kadare, and Rodriguez and further in view of Wimmer et al. (US 2002/0098202). The Applicants respectfully traverse this rejection.

Claims 8-10 are a directed to a method that comprises determining an effect of the candidate agent on HCV replication.

In making this rejection the Examiner has stated that while the teachings of Del Vecchio, Jin, Kadare, and Rodriguez render obvious the identification of HCV inhibitors through identification of NS4B GTPase inhibitors, the references do not teach or suggest testing effect of GTPase inhibitors on HCV replication. The Examiner states that Wimmer corrects this deficiency.

The Applicants believe that claims 8-10 are patentable because, at the time of filing, the function of NS4B, particularly the role of NS4B's GTPase activity in HCV replication, was unknown.

Support for this position is found in several reviews which the Applicants believe adequately represent the state of the art at the time of filing (See reviews by Rosenberg, J. Mol. Biol. 2001 313: 451-64, Exhibit D; and by Kato Acta. Med. Okayama, 2001, 55: 133-159, Exhibit E). For example Kato in a review article in Acta. Med. Okayama, 2001, Vol. 55. No. 3, pp.133-159 states that:

> NS4B protein (261 amino acid residues for HCV-1b) is rich in hydrophobic amino acid residues and has been detected primarily in the membrane fraction [36, 39]. The function of the NS4B protein remains unknown, although it has been recently demonstrated that the NS4B protein in association with the Ha-ras gene played an important role in the malignant transformation of NIH3T3 cells [223].

and Rosenberg in J. Mol. Biol., 2001, Oct 26; 313(3):451-64 states that:

> Two of the non-structural proteins, NS4b and NS5a, are still of unknown function.

In fact, this position is supported by Del Veccio and Wimmer – two references that are cited *in support* of this rejection.

Del Vecchio on page 3, Table 1 and lines 9-10 states that

> Press, New York (1996)). However, the function of HCV NS4B protein, like that of the NS4B in the other members of the *Flaviviridae* family, is still unknown.

and Wimmer on page 1, paragraph 5 states that:

tor of the NS3 proteinase. The functions of NS4B and p7 proteins are so far unknown. NS5B is identified as the

While the Applicants understand that there are a finite number of assays by which NS4B's function can be tested, the number of these assays is quite high and includes assays for transcription, translation, protein degradation, protein folding, protein transport, nucleotide metabolism, cell metabolism, immune system evasion, to name but a few. Alternatively, NS4B may be non-essential for any part of the viral lifecycle. Thus one of skill in the art would not have a reasonable expectation that the GTPase activity of NS4B protein was required for HCV replication.

The Examiner may try to argue that it would be obvious to one of skill in the art to try various assays to ascribe a function to the NS4B protein and, as such, its role in replication would have been obvious. According to the Obviousness Guidelines, however, when Office personnel reject claims using "obvious to try" rationale, the Office must resolve the Graham factual inquiries and articulate:

(1) "a finding that at the time of the invention, there had been a recognized problem or need in the art";

(2) "a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem";

(3) "a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success." (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57532, citing KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395 (US 2007).

Thus, in order to render claims obvious using an "obvious to try" standard, there must also be a reasonable expectation of success. In this case, the function of NS4B was unknown, and there were tens if not hundreds of assays by which the function of NS4B could be tested. Since none of the assays would have a reasonable expectation of success in identifying the function of NS4B, the Examiner cannot reject claims 8-10 using an "obvious to try" standard.

In view of the foregoing discussion, the Applicants submit that the cited references in any combination do not establish a prima facie case of obviousness. Thus the 103(a) rejection does not apply and as such should be withdrawn.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone James Keddie at (650) 833-7723.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-316.

Respectfully submitted,
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